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White matter microstructure of the extended limbic system in male and female youth with conduct disorder

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Abstract

Background: Previous studies of conduct disorder (CD) have reported structural and functional alterations in the limbic system. However, the white matter tracts that connect limbic regions have not been comprehensively studied. The uncinate fasciculus (UF), a tract connecting limbic to prefrontal regions, has been implicated in CD. However, CD-related alterations in other limbic tracts, such as the cingulum and the fornix, have not been investigated. Furthermore, few studies have examined the influence of sex and none have been adequately powered to test whether the relationship between CD and structural connectivity differs by sex. We examined whether adolescent males and females with CD exhibit differences in structural connectivity compared to typically-developing controls.

Methods: We acquired diffusion-weighted MRI data from 101 adolescents with CD (52 females) and 99 controls (50 females). Data were processed for deterministic spherical deconvolution tractography. Virtual dissections of the UF, the three subdivisions of the cingulum (retrosplenial, parahippocampal and subgenual cingulum), and the fornix were performed and measures of fractional anisotropy (FA) and hindrance-modulated orientational anisotropy (HMOA) were analysed.

Results: The CD group had lower FA and HMOA in the right retrosplenial cingulum tract relative to controls. Importantly, these effects were moderated by sex - males with CD significantly lower FA compared to male controls, whereas CD and control females did not differ.

Conclusions: Our results highlight the importance of considering sex when studying the neurobiological basis of CD. Sex differences in retrosplenial cingulum connectivity may contribute to sex differences in the clinical presentation of CD.

Word count abstract: 248

1 Introduction

2 Conduct Disorder (CD) is diagnosed in children and adolescents who display a pattern of behaviour in 3 which societal rules and the rights of others are violated (American Psychiatric Association, 2013). 4 Although the lifetime prevalence of CD is higher amongst males than females (by a ratio of 5 approximately 2.4:1), it is increasingly prevalent in adolescent females. Individuals with CD have 6 poor prognoses with negative adult outcomes that include criminality, alcohol abuse, unemployment, 7 and poor mental and physical health. CD is one of the main reasons for referral to child and 8 adolescent mental health services, and places a high burden on the affected individuals, families and 9 society in general. Therefore, CD can be considered a major mental and public health priority and 10 gaining a better understanding of its neurodevelopmental underpinnings is critical.

11

12 It has been proposed that limbic system dysfunction may underlie antisocial behaviour. Brain regions 13 that make up the limbic system include the anterior cingulate cortex (ACC) and posterior cingulate 14 cortex (PCC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), hippocampus, 15 hypothalamus, amygdala, and medial temporal lobe (Rolls, 2004, 2013). The limbic system is 16 involved in emotion processing and regulation, reward-related decision-making and a range of other 17 cognitive functions (Blair, 2008). Evidence implicating limbic brain structures in antisocial behaviour 18 comes from a number of sources. Two structural magnetic resonance imaging (sMRI) meta-analyses 19 concluded that the most robust abnormalities in grey matter volumes observed in this population are 20 in limbic brain structures, such as the amygdala, ACC and vmPFC (Aoki et al., 2014; Raschle et al., 21 2015; Rogers and De Brito, 2016). In line with this, a recent meta-analysis of fMRI studies reported 22 that CD individuals consistently displayed underactivation in the ACC and vmPFC during tasks 23 involving emotion processing, and 'hot' (motivationally-relevant) executive functions, and in 24 dorsolateral prefrontal cortex (dlPFC), dorsal ACC, and hippocampus during 'cool' (non-affective) 25 executive function tasks (Alegria et al., 2016).

26

27 Given this evidence for structural alterations and abnormal neural activity in limbic regions in 28 individuals with CD, it is possible that the structural connections linking these regions are also 29 compromised. The major limbic system white matter (WM) pathways include the fornix, the 30 cingulum, and the uncinate fasciculus (UF; Catani et al., 2013). Structural connectivity and the micro-31 structural properties of brain tissue are frequently assessed using diffusion tensor imaging (DTI) 32 techniques (Catani and Thiebaut de Schotten, 2012). However, previous DTI studies in youths with 33 CD and related disorders have had several limitations. First, the majority of DTI studies in CD have 34 focused on males (although see Menks et al., 2017). Therefore, possible sex differences in the 35 microstructural integrity of limbic system-related tracts have not been investigated. This is important 36 as the neurobiological basis of CD has been shown to differ in several respects between males and

females (Fairchild et al., 2013; Decety et al., 2015; Smaragdi et al., 2017). Only one small study directly compared males and females with CD (n=14 and 13, respectively) in terms of WM microstructure (Zhang et al., 2014). It investigated fractional anisotropy (FA) values of the UF using deterministic tractography (which investigates specific anatomical pathways). Interestingly, the authors found higher FA values in the UF in males, but not females, with CD. These preliminary findings suggest that WM microstructural alterations in temporo-frontal regions might be specific to males with CD.

44

45 Additionally, aside from one very recent study (Sethi et al., 2018), previous studies using DTI-based 46 tractography methods in individuals with CD have largely focused on the UF tract (Passamonti et al., 47 2012; Sarkar et al., 2013; Zhang, Gao, et al., 2014). The fact that these studies focused on this tract 48 may have been due to earlier studies in adults with antisocial personality disorder (ASPD; an adult 49 condition of which CD is an antecedent) and psychopathy, finding lower FA in the UF in these 50 individuals compared to healthy controls (Craig et al., 2009). However, opposite findings have been 51 reported in youths with CD, who show higher FA values in the UF relative to healthy controls 52 (Passamonti et al., 2012; Sarkar et al., 2013; Zhang, Gao, et al., 2014). Similarly, a study 53 investigating the dorsal and ventral components of the cingulum tract, reported lower radial 54 diffusivity (RD) in the dorsal cingulum bundle in individuals with CD compared to controls (Sethi et 55 al., 2018). This was opposite to the pattern observed in adults with ASPD (Sethi et al., 2014). Several 56 authors have suggested that the opposite patterns observed in WM microstructural measures in youths 57 and adults might be due to abnormally accelerated maturation of WM tracts in individuals with CD 58 (Passamonti et al., 2012; Sarkar et al., 2013b; Zhang, Gao, et al., 2014). Although these previous 59 studies were important first steps in understanding CD-related alterations in structural connectivity, 60 the focus of research needs to be expanded to consider additional limbic system tracts. It is also 61 important to test whether alterations in WM microstructure are common or distinct across males and 62 females with CD.

63

64 An additional limitation of prior studies is that they used either tractography methods or a 65 characterization of WM diffusivity exclusively based on the diffusion tensor model. Although the 66 diffusion tensor model is most frequently used to reconstruct WM tracts and characterise diffusivity in 67 WM (Basser et al., 2000), this approach has several limitations. First, it is not well-suited for studying 68 complex fibre configurations such as crossing fibres, branching regions or intra-voxel combinations 69 of different tissue types (e.g., WM fibres and grey matter). Second, while FA is the most commonly 70 used index to quantify water diffusivity in studies using tensor-based models, it is calculated at a 71 voxel level and is determined by several microstructural and macrostructural features, such as 72 myelination of WM fibres, size and packing density of cells and number of crossing fibres 73 (Vanderauwera et al., 2015). Thus, partial volume effects (i.e., not fibre- or tissue -specific) can affect

74 DTI indices (e.g., FA, RD), and voxel-average diffusion MRI parameters such as FA, lack within-75 voxel single fibre population specificity (Dell'Acqua et al., 2013; Raffelt et al., 2015). Novel non-76 tensor models such as constrained spherical deconvolution (SD) have the potential to overcome these 77 limitations and more accurately characterise the underlying architecture of specific WM tracts 78 (Dell'Acqua et al., 2010). In addition, the hindrance-modulated orientational anisotropy (HMOA) 79 index that can be derived using SD algorithms provides greater sensitivity in terms of detecting 80 microstructural changes in specific WM tracts than FA (Dell'Acqua et al., 2013). Finally, most 81 previous DTI studies included relatively small samples - typically groups of 15 participants or fewer 82 (Sethi et al., 2018; Finger et al., 2012; Haney-Caron et al., 2014; Passamonti et al., 2012; Zhang, Gao, 83 et al., 2014).

84

85 The present study addresses a number of these limitations, and extends previous findings by, first, 86 examining sex differences in the relationship between CD and WM microstructure. Second, by 87 examining two key limbic WM tracts overlooked in prior studies: the fornix and the cingulum 88 bundles - the retrosplenial (RSC), parahippocampal (PHC) and subgenual cingulum (SGC; Jones et 89 al., 2013) - as tracts plausibly involved in the pathophysiology of CD. Third, by enhancing statistical 90 power and the robustness of our results by substantially increasing the sample size compared to 91 previous studies. Finally, by employing a novel method – constrained SD. Recent studies have 92 compared tensor versus non-tensor models in clinical samples and suggested that the latter approach 93 provides more accurate and robust results (Auriat et al., 2015). However, to increase comparability 94 with previous studies, we also estimated indices of FA - the most widely-used parameter in previous 95 structural connectivity research.

96

97 We hypothesised that differences between CD and control groups would be most evident in limbic 98 tracts involved in socio-emotional processes (i.e., subgenual cingulum, retrosplenial cingulum, and 99 UF) in comparison with posterior and lateral limbic WM tracts (e.g., parahippocampal cingulum). We 100 also hypothesised that CD-related alterations in WM microstructure would be most evident in males 101 (Zhang et al., 2014). In addition, recent DTI studies have shown that individuals with CD and 102 elevated callous-unemotional (CU) traits may differ from those with low levels of CU traits in terms of WM microstructural abnormalities (Sethi et al., 2018; Puzzo et al., 2017). Thus, we also 103 104 investigated whether CU traits contributed to the WM microstructural alterations observed in CD. We 105 also tested for correlations between WM measures and the grandiose-manipulative and impulsive-106 irresponsible subdimensions of psychopathy and CD symptoms.

107 Methods

108 **Participants**

- 109
- 110 Participants for this study were recruited at four different sites involved in the Neurobiology and
- 111 Treatment of Female Conduct Disorder (FemNAT-CD; www.femnat-cd.eu) study University of
- 112 Southampton, University of Birmingham, University Hospital Aachen, and University of Basel. All
- 113 participants and the majority of their parents underwent a diagnostic interview that was based on
- 114 DSM-IV criteria (the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and
- 115 Lifetime; Kaufman et al., 1997). At the UK sites, IQ was assessed using the two subtest form of the
- 116 Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) whereas the German version of the
- 117 Wechsler Intelligence Scale for Children (Wechsler, 2003) was used at the other sites. The t and
- 118 standard scores from all sites were transformed into z-scores and then combined to yield estimates of
- 119 full-scale IQ.

120 The Match program (Van Casteren and Davis, 2007) was used to select an IQ-, age- and gender-121 matched sample from the subset of participants for whom diffusion MRI data were available (n=325). 122 There are dramatic changes in WM development across childhood and adolescence (Casey et al., 123 2008), thus we excluded children aged 9-12 years (n=57; see Supplementary Material for more 124 information). A total sample of 200 adolescents (101 with conduct disorder (52 females) and 99 125 healthy controls (50 females) was included in the present analyses – all aged 13-18 years. The Youth 126 Psychopathic traits Inventory (YPI; Andershed et al., 2002); a self-report questionnaire assessing 127 overall psychopathic traits and sub-dimensions of psychopathy, and the parent-report Inventory of 128 Callous Unemotional traits (ICU; Essau, Sasagawa and Frick, 2006); a standardized measure 129 including callous, uncaring and unemotional subscales, were used to assess psychopathic and callous-130 unemotional (CU) traits, respectively.

131 Diffusion-weighted MRI data acquisition

132

133 Diffusion-weighted MRI data were acquired with the following parameters: Repetition time (TR) = 134 8000ms (Achieva), 8800ms (Tim-Trio), 7500ms (Prisma); echo-time (TE) = 87ms (Achieva), 92ms 135 (Tim-Trio), 71ms (Prisma) and a bandwidth of 1633.3 Hz/Px (Achieva) or 1776 Hz/Px (Tim-Trio & 136 Prisma); echo-spacing = 0.75ms (Achieva), 0.73ms (Tim-Trio), 0.65ms (Prisma); slice thickness = 137 2.0mm; field of view (FOV) = $256 \times 256 \times 124$ mm; acquisition matrix = 128×128 ; voxel-size = 138 $2 \times 2 \times 2$ mm; 62 contiguous axial slices (no slice gap). Images were acquired with diffusion gradients 139 (b-value=1500 s/mm²) applied in 64 non coplanar and non collinear directions and two b-value=0 140 (s/mm²) volumes with reversed phase encoding (blip-up/blip-down), yielding pairs of images with 141 distortions in opposite phase-encode directions to enable accurate estimation and correction for 142 susceptibility-induced distortions.

143

144 **Pre-processing**

145

146 Datasets were corrected for head motion and eddy current distortions using FSL (Andersson and 147 Sotiropoulos, 2016). Distortions in the magnetic field were estimated. The estimated field was 148 subsequently used, together with all the diffusion data, to estimate eddy current-induced distortions 149 and subject movement (Andersson and Sotiropoulos, 2016). Movement-induced signal dropout was 150 identified and the lost signal was replaced by a non-parametric Q-space interpolation (Andersson et 151 al., 2016).

152

153 Spherical deconvolution was calculated using the damped Richardson-Lucy algorithm (Dell'Acqua et

al., 2010) with a fibre response parameter of $\alpha = 1.5$, 400 algorithm iterations, threshold parameters of 0.06, and a harmonic order of 8 (lmax=8). An absolute (0.1%) and relative (5%) threshold on the

156 Fibre Orientation Distribution (FOD) amplitude were applied to exclude spurious local connections

- 157 (Dell'Acqua et al., 2013).
- 158

Whole brain deterministic tractography was performed using a step size of 0.5mm with a limit set to display streamlines between 20 and 400 mm. The Euler algorithm was used to follow the orientation vector of least curvature (angle threshold of 45°). Spherical deconvolution and tractography analysis was performed using StarTrack software (<u>https://www.mr-startrack.com/</u>). Explore DTI was used for the tensor fit. Tensor-derived FA and HMOA values of WM microstructural organisation were exported to TrackVis. We report FA values in the present study for the purpose of increasing comparability with previous studies.

166

167 **Delineation of Regions of Interest**

168 TrackVis was used to reconstruct the fornix, cingulum bundle subdivisions and UF. Reconstruction of 169 these tracts has previously been described (fornix and UF: (Stieltjes et al., 2013), and CB 170 subdivisions: (Jones et al., 2013)). The Boolean logic (AND, and NOT gates) was employed to 171 delineate the CB's subdivisions, the fornix and the UF (Figure 1 shows the reconstruction for all of 172 the limbic WM tracts).

173

174 Statistical analysis

175 Matlab_R2016 was used to carry out statistical analysis. Shapiro-Wilk tests were used to verify

176 normality of HMOA and FA values across subjects.. Tract measures of HMOA and FA were analysed

177 using a general linear model (GLM) to test for effects of diagnosis and sex-by-diagnosis interactions.

The GLM included the following covariates which have been shown to be associated with WM microstructural integrity in adolescent studies: age (Asato et al., 2010), IQ (Dunst et al., 2014), and site (coded as binary fixed effect). Where significant sex-by-diagnosis interactions were found, we followed these up by comparing FA and HMOA values between CD and healthy control males, and between CD and healthy control females.

183

ADHD is a neurodevelopmental disorder that frequently co-occurs with CD, and previous DTI studies have shown that comorbid ADHD strongly modulates WM effects (Wang et al., 2012). Thus, we repeated the GLM analysis while adding current ADHD symptoms (i.e., those displayed in the last year) as an additional covariate.

188

189 In addition, there is some evidence for structural differences between the childhood–onset (CO) and 190 adolescent-onset (AO) variants of CD (Fairchild et al., 2015). Accordingly, we used the same model

191 to compare these subgroups, to assess the validity of combining these subgroups in our main analysis.

192

193 The significance threshold was adjusted using the Benjamin–Hochberg false discovery rate (FDR:

- 194 q < 0.05) correction for multiple comparisons across each parameter independently. Effect sizes for
- 195 diagnosis effects were calculated using Cohen's d and effect sizes for sex-by-diagnosis interactions
- 196 were expressed as partial eta-squared (ηp^2) .

197 In cases where significant main effects of diagnosis were observed, we followed these up by running 198 a GLM analysis (only in the CD group), to test for associations between CD symptoms, psychopathy 199 (YPI total), dimensions of psychopathic traits (grandiose-manipulative, and impulsive-irresponsible 200 traits), CU traits (YPI subscale and ICU total), ICU subscales (callousness, uncaring, unemotional), 201 and measures of HMOA and FA. Lastly, given that the CD sample included many individuals with 202 comorbid ADHD, we also explored the relationship between ADHD symptoms and measures of 203 HMOA and FA. These correlational analyses were run in a mixed-sex CD group (males and females 204 with CD) as well as in each sex separately.

205

206 Results

207 Demographic Variables

Individuals in the CD group had significantly more CD, ODD, and ADHD symptoms than healthy controls. They also scored higher in overall psychopathic traits, as well as callous-unemotional, grandiose and manipulative, and impulsive and irresponsible subdimensions of psychopathy (Table

- 211 1). There were no significant differences between males and females in the age-of-onset of CD (i.e.,
- 212 childhood-onset vs. adolescent-onset).
- 213
- 214 In terms of psychiatric comorbidity in individuals with CD, males and females differed only in rates
- 215 of substance abuse (M>F); there were no other significant differences between males and females.
- 216 Finally, there was an unequal sample distribution across the sites (see Supplementary Table 1). To
- address this issue, we included site as a covariate of no interest.
- 218

219 Tractography results

- 220 There were no significant differences between the CO-CD and AO-CD subtypes in HMOA or FA in
- any WM tract.
- 222

223 Main effects of diagnosis

Relative to controls, individuals with CD had lower HMOA in bilateral retrosplenial cingulum (RSC; right: t(190)=-2.22, p=0.03, d=0.10; left: t(190)=-2.27, p=0.02, d=0.16), and lower FA in the right RSC (t(190)=-2.91, p=0.004, d=0.28). However, after correcting for multiple comparisons, only the effect on right RSC FA remained significant (pFDR=.03; Figure 2). There were no significant group differences in HMOA or FA in any of the other limbic WM tracts.

229

230 Sex-by-diagnosis interactions

231 We observed sex-by-diagnosis interactions for HMOA in bilateral RSC (right: t(190)=2.08, p=0.04, 232 $\eta p^2 = 0.02$: left: t(190)=1.99, p=0.05, $\eta p^2 = 0.02$), and FA in right RSC (t(190)=2.75, p=0.006, 233 $\eta p^2 = 0.04$). All interactions followed the same pattern: males with CD showed lower values than male 234 controls, whereas females with CD showed higher values than female controls (Figure 3). However, 235 only the sex-by-diagnosis interaction for right RSC FA survived correction for multiple comparisons 236 (pFDR=.05). No other significant interaction effects were found in the other limbic tracts (see 237 Supplementary Table 2). Post-hoc analysis showed that relative to male controls, CD males had lower 238 HMOA in bilateral retrosplenial cingulum (RSC; right: t(190)=-2.52, p=0.04, d=0.39; left: t(190)=-239 1.99, p=0.04, d=0.37) and lower FA in the right RSC (t(190)=-2.91, p=0.01, d=0.47). However, after 240 correcting for multiple comparisons, only the effect in right RSC FA remained significant 241 (pFDR=.03). There were no significant differences between female CD and control groups.

242

243 ADHD comorbidity as a potential confound

244 The main effects of diagnosis observed for FA in the right RSC (p=0.03) and for HMOA in bilateral

245 RSC (left: p=0.05: right: p=0.05) in CD versus healthy control males remained significant after

factoring out current ADHD symptoms. However, only the group difference in right RSC FA remained significant (pFDR=0.03) after correcting for multiple comparisons. Moreover, significant main effects of diagnosis emerged in the right UF when factoring out ADHD symptoms: participants with CD showed lower FA (t(189)=2.00, p=0.05, pFDR=0.05), and HMOA (t(189)=2.07, p=0.04, pFDR=0.05; Figure S1) relative to healthy controls. Unlike the findings for the RSC, this main effect

- 251 of diagnosis in the UF was not qualified by a significant sex-by-diagnosis interaction.
- 252

253 Correlations between structural connectivity measures and CD symptoms, ADHD symptoms, 254 and psychopathic or callous-unemotional traits

255

256 Within the CD sample, there was a positive correlation between current CD symptoms and right RSC

HMOA (r=.36, pFDR=0.02; Figure 4). There were no other significant correlations between CD,

ADHD symptoms, overall psychopathic traits, the subdimensions of psychopathy, CU traits or the

- 259 ICU subscales (Callousness, Uncaring, Unemotional) and measures of WM in other tracts.
- 260

261 As effects of diagnosis were found in males, but not in females with CD, we conducted correlational 262 analyses in males and female groups separately. A strong positive correlation between current CD 263 symptoms (r=.45, pFDR=0.002; Figure S2), and a negative correlation between current ADHD 264 symptoms (r= -.31, pFDR=0.03; Figure S3) and right RSC HMOA was found in the male CD group. 265 No effects of CU or psychopathic traits were observed in CD males. No significant correlations were 266 found between clinical symptoms or CU/psychopathic traits or subscales and measures of structural 267 connectivity in females with CD. Moreover, there were no significant sex-by-CD symptoms or sex-268 by-CU/psychopathic traits interactions for either HMOA or FA.

269

270

271 Discussion

272 Abnormalities in the limbic system have been consistently implicated in the pathophysiology of CD 273 (Alegria et al., 2016; Raschle et al., 2015; Rogers and De Brito, 2016). We extended the DTI 274 literature by including female participants and a much larger sample than has been studied to date 275 (N=200). This allowed us to test whether females and males with CD show common or distinct 276 alterations in limbic WM microstructure. We also investigated limbic WM tracts beyond the UF and 277 capitalised on recent methodological advances in diffusion-weighted image processing by employing 278 spherical deconvolution (SD) models. This approach provides a more reliable estimation of multiple 279 fibres passing through a voxel with distinct orientations.

280

Our findings extend knowledge regarding alterations in limbic WM tracts in CD and support the hypothesis that abnormalities in fronto-limbic tracts are involved in the pathophysiology of this disorder. However, such abnormalities appear to be limited to males with CD – no such effects were found in females. More specifically, only males with CD showed lower FA in the right RSC relative to male controls. In fact, there was a suggestion that the opposite pattern was observed in females (females with CD appeared to show higher FA and HMOA values relative to control females) – although this was not statistically significant.

288

289 Previous DTI studies have found structural abnormalities in regions that overlap with the RSC. A 290 recent study using a similar approach to the present study (i.e., region of interest-based tractography) 291 investigated dorsal and ventral cingulum WM microstructure in male youths with CD (Sethi et al., 292 2018). Lower RD values were observed in bilateral dorsal cingulum in the CD group relative to 293 controls (Sethi et al., 2018). FA values normally increase when RD decreases, and the opposite 294 pattern seems associated with myelin loss and axonal abnormalities (Harsan et al., 2006). Although 295 the anatomical delineation of the cingulum bundle differed between the two studies (i.e., dorsal and 296 ventral in Sethi et al. versus retrosplenial, parahippocampal and subgenual cingulum in the present 297 study), the dorsal part of the cingulum overlaps most closely with the RSC tract compared to the other 298 cingulum bundles – thus the findings are congruent in terms of location, but not in the direction of the 299 effects. In addition, the Sethi et al. (2018) study differs from the present study in the use of tensor-300 based models versus non-tensor models.

301

302 The RSC is composed of fibres that connect the medial prefrontal cortex, dlPFC, ACC, PCC, medial 303 temporal lobe, and angular gyrus together (Jones et al., 2013). These regions have been associated 304 with social-emotional processing, self-reflection, executive functions and moral decision-making. 305 They are key nodes of the default mode network (DMN) that is responsible for self-referential 306 processing (Leech et al., 2012). Previous studies investigating DMN connectivity in youths with CD 307 have reported reduced connectivity between core DMN regions including the medial PFC, PCC, 308 precuneus and superior temporal gyrus, relative to controls (Broulidakis et al., 2016; Zhou et al., 309 2016). It has been proposed that DMN dysfunction in CD may reflect delays in the development of 310 brain circuits linked to self-awareness, regulating emotions, moral judgments and future planning 311 (Zhou et al., 2015). Impairments in these processes have been reported in CD (e.g. White et al., 2014). 312 The RSC connects core regions that make up the DMN. Thus, the abnormal functional connectivity of 313 the DMN observed in previous studies may have a structural basis in altered RSC connectivity.

314

Although group differences in FA in the UF only became significant after controlling for comorbid ADHD symptoms, our results are in contrast to findings reported by Zhang et al. (2014). We did not observe any sex-by-diagnosis interactions in this WM tract. Both males and females with CD 318 appeared to be equally affected in terms of showing lower UF FA. However, in line with Zhang et al.

319 (2014), we also observed sex differences in the RSC tract in youths with CD. Males with CD showed

320 lower FA (and HMOA at an uncorrected level) relative to sex-matched healthy controls, whereas

321 there were no significant differences between CD and control females.

Previous DTI studies of CD have observed higher FA values in male-only samples, suggesting accelerated maturation in individuals with CD. Here, we observed lower FA in males with CD compared to male controls. Although the results observed here were in a previously unstudied tract, it suggests that WM maturation is delayed in males with CD. Delayed maturation of WM is associated with poor inhibitory control (Simmonds et al., 2014) - a key feature of CD.

327

328 Furthermore, our correlational analyses showed that CD symptoms were significantly (positively) 329 correlated with HMOA of the right RSC tract in males, but not females. Therefore, the present study 330 provides new evidence for sex differences in the neurobiological basis of CD - RSC WM 331 abnormalities were observed in males but not females. We also observed a significant negative 332 correlation between ADHD symptoms and HMOA in the right RSC tract in males but not females, 333 indicating that ADHD comorbidity may have influenced the differences between CD and control 334 males in the RSC. This is of significance due to the substantial overlap of ADHD and CD, and 335 symptom dimensions related to ADHD such as impulsivity and hyperactivity have been associated 336 with the development of antisocial behaviour in childhood (Barkley et al., 2004).

337 Several neuropsychological studies investigating aspects of executive functioning (i.e., assessing 338 inhibition/attention and decision-making), are consistent with our findings by showing divergent 339 results in males and females with CD. Males with CD exhibit deficits in reversal learning (Herpertz et 340 al., 2008) and differ in terms of decision-making (e.g., making more risky choices) relative to control 341 males, whereas CD females do not differ from control females (Sidlauskaite et al., 2017). In addition, 342 our finding of a sex-by-diagnosis interaction in the RSC highlights the importance of taking sex into 343 account when studying the neurobiology of CD, and the problems that might arise when combining 344 males and females with CD in the same group (Smaragdi et al., 2017). Future studies should 345 investigate the functional consequences of altered RSC structural connectivity in males and females 346 with CD by employing resting state functional connectivity methods, and by using 347 neuropsychological tasks tapping decision-making and empathic processes in the same sample.

348

349 Strengths and limitations

350

The strengths of this study include the investigation of additional limbic WM tracts by using a more comprehensive approach – SD tractography. The main benefit of this approach is to resolve fibre353 crossing issues. In addition, SD techniques improve the accuracy of fibre tracking compared to 354 models based on the diffusion tensor alone (Dell'Acqua et al., 2010). Secondly, the comparatively 355 large sample size in the present study (N=200), which included males and females with and without 356 CD, allowed us, for the first time, to comprehensively investigate sex differences in the relationship 357 between CD and structural connectivity. Another strength is the fact that the CD group was assessed 358 using standardised, semi-structured interviews based on DSM-IV criteria as well as obtaining detailed 359 information about comorbid disorders and accounting for ADHD comorbidity in our statistical 360 analyses.

361

362 However, our study also had several limitations. First, the sample ranged in age from 13-18 years. 363 The CD and control groups did not differ in age; however, age is known to have an important effect 364 on white matter development. Thus, we included age as a covariate of no interest in all analyses. 365 Second, the sex distribution across the sites was uneven (more girls were tested at some sites than 366 others), and although quality control procedures were performed prior to starting data acquisition 367 (e.g., matching acquisition parameters and going through a site qualification process), combining data 368 from different sites and scanner manufacturers (Phillips and Siemens) may introduce unintended 369 variability. However, to reduce the impact of this variability, all analyses included site as a covariate 370 of no interest. Finally, although we used SD methods to reconstruct the WM tracts, indices of FA 371 were derived from tensor-based models fitted to b=1500 diffusion-weighted data and projected onto 372 the SD-derived tracts. Hence there is a potential source of variability in terms of comparing the 373 present FA measures with those reported in previous studies, although several earlier studies adopted 374 a similar approach (e.g., Christiansen et al., 2016, Rojkova et al., 2016).

375

376 In conclusion, we found that male adolescents with CD differed from healthy controls in retrosplenial 377 cingulum white matter microstructure – showing lower FA and HMOA values in this tract. This effect 378 was not seen in females with CD. These differences in structural connectivity may help explain sex 379 differences in CD and its clinical presentation. Given the overlap of the RSC tract with brain regions 380 that constitute the DMN, and its role in connecting these regions together, future studies should 381 investigate whether there are sex differences in DMN functional connectivity in CD. This would 382 improve our understanding of the pathophysiology of CD and could lead to improved diagnosis and 383 treatments for both sexes.

384

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390

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395

396 Conflicts of interest

- 397 Prof. Freitag receives royalties for books on Attention-Deficit/Hyperactivity Disorder and Autism
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- 412
- 413

414 **Ethical standards**

- The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki
- 417 Declaration of 1975, as revised in 2008.
- 418
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- 420
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